# Applicant's Reliance on the application of current EFSA Guidance documents

**(e.g. human relevance assessment of T-Modality, ECHA/EFSA Guidance, 2018)**

MEETING WITH EFSA - 15 DECEMBER 2025

# Appendix A and EFSA Recurring Issues 2025

The ECHA/EFSA GD (2018) Appendix A acknowledges qualitative and quantitative species differences in the thyroid hormone system

Proposals are made how to investigate compounds inducing liver mediated thyroid toxicity

- Non-human relevance testing using the in vitro comparative liver enzyme induction assay (CIVHE)
- Use Weight of Evidence of all of the available data
- Higher Tier testing in offspring animals

Up to now human non-relevance has never been the reason for concluding on No ED for the T-modality

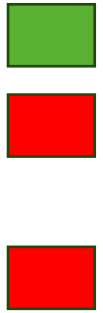
Recurring Issues, 2025

Provides some guidance on how to conduct and assess the CIVHE

No decision, how to assess the biological relevance of human hepatocyte data

Defines CTA (Comparative Thyroid Assay) as gold standard for follow up testing

No guidance, how to evaluate the assay, but some critical issues (see next slide)



# EFSA Recurring Issues, 2025 confirms

Overall, regarding the recurrent submission of studies to test hepatic phase II enzyme induction, EFSA is of the opinion that:

- the submitted strategy, with studies not conducted under good laboratory practice (GLP) and based on non-guideline studies, needs experts' assessment and critical appraisal on a case-by-case scenario. Reliability and robustness of the study need to be addressed, and results need to be considered in a WoE approach with the overall data. No conclusion based solely on this study would be possible.
- The relevance of the method to assess the induction of hepatic phase II enzymes still needs to be proven.

**Question: What is a sufficiently high WoE to conclude on ED and human non-relevance using animal and non-animal data?**

Therefore, in EFSA's experience, the CTA study is considered the gold standard to assess the HPT axis perturbation; however, since the ECHA/EFSA guidance entered into force, it has been requested in a few cases to substantiate the pattern of T-mediated adversity. EFSA acknowledged that:

- the CTA is not a data requirement in the PPP regulation, and there is no OECD TG;
- the CTA study poses some challenges in terms of measurement of thyroid histopathology in fetuses, analytical methods for TH measurements, and the need to include a positive standard like PTU (Propylthiouracil);
- on some occasions, sample timing and endpoints from the CTA study protocol were included in the OECD TG 443 study design; nevertheless, this is not a recommended option as it would increase the complexity of an already demanding study protocol.

**CTA as gold standard - Points to consider**

- Study does **not** address the endpoint of concern (neurological deficits)
- Developed for risk assessment → unclear how to evaluate for hazard identification
- Confounded by systemic toxicity at highest dose level > MTD
- CTA uses > 2000 animals, while there is strong encouragement to avoid animal testing and use NAMs

# Open technical dialogue between experts proposed

**Define together, what is a sufficiently high WoE to conclude on**
**ED – yes**
**ED - no**

Retrospective analysis could help on e.g.:

- Level of adversity
- Level of T4 changes, that triggered further testing – alignment between EFSA and MS
- Outcome of DNT/CTA

An update of Appendix A to clarify criteria for WoE including a flow-chart would be helpful

Technical Exchange between EFSA and Company technical Experts on e.g. anonymized data sets – main topics

**Comparative in vitro liver enzyme induction assay**

- Study design (no. Species, donors, evaluation)
- Reference compounds
- Biological relevance for humans

**Comparative Modeling / PBK Modeling**

- Validation / acceptance
- Establish communication with EFSA Modeling Group / involve Member States
- CLE Webinar (involving Modeling Experts) planned

**Offspring Animal data – higher tier studies**

- Evaluation Criteria for the CTA for hazard purposes
- Exchange on adapted design of the CTA
- Assessment of DNT data, if available

**Which uncertainties in the data set are acceptable?**

# CLE Position on the EFSA Non-target terrestrial organisms Specific Protection Goals Strategy

**MANAGING THE ACCEPTABILITY OF ENVIRONMENTAL RISKS**

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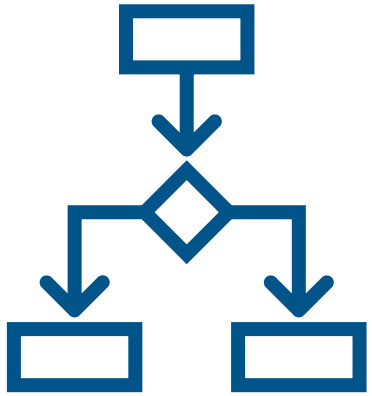
# General points

## The pesticide regulatory framework must be proportionate ensure farmers' access to effective PPP tools

**Simplification.** Align with Commission simplification agenda to ensure simple and workable risk assessment methodology for EFSA, Member State authorities and applicants. The recently published efsa proposed risk assessment protocol is highly complex and conservative and is likely to lead to a reduction in farmers access to essential plant protection products (PPPs).

**Risk management.** Include more risk management options within the Risk assessment framework than just "no approval" to ensure SPGs enable risk management instead of limiting it. A too narrow focus on environmental effects leads to the setting of highly conservative SPGs that limit options for risk managers to manage risks to acceptable levels.

**European Commission mandate.** Ensure alignment with the issued Commission mandates for the setting of SPGs and the development of the risk assessment methodology that considers "…their practical feasibility and thus their impact on workload of risk assessors. Particular attention should be given to develop proportionate and flexible methodologies…."

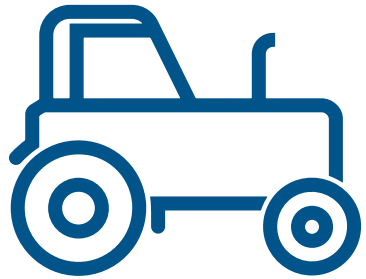


# Managing the acceptability of environmental risks

## Consider the context of PPP use for risk assessment guidance and SPGs

**Benefits to agricultural production.** The production of food, feed and other agricultural products should be recognized as the primary ecosystem service of agricultural fields. The benefits of PPPs to this ecosystem service should be recognised to allow risk managers to make an informed decision on the acceptability of PPP risks.

**Effects of other tools and practices.** The effects of PPPs should be assessed in the context of the effects of other agricultural tools and practices (e.g., ploughing, harvesting and fertilization) used in integrated crop management (ICM) systems.



**Effects of alternatives to PPPs.** The effects of PPP use should be benchmarked against the effects of alternatives (e.g., other PPPs, ploughing for weed control, physical treatments against pest and diseases) to assess the acceptability of PPP risks.

**Alternatives for biodiversity conservation and restoration.** There are many options for nature conservation and restoration (e.g., habitat creation, climate change mitigation, invasive species management) other than pesticide regulation. The alternatives in the existing policy and regulatory framework for biodiversity conservation and restoration should also be considered.

# SPGs that allow risk management decisions

## Set agronomically realistic SPGs considering the context in which PPPs are used

**Effects of agriculture.** Allow for medium to large in-field and edge of field effects for non-target arthropods (NTAs) and soil organisms to reflect the medium to large effects of agriculture and to align with the efficacy requirements of Regulation 1107/2009.

**Recovery.** Allow for recovery of NTAs and soil organisms since recovery is the baseline in highly disturbed agricultural ecosystems.

**Ecosystem service provisioning.** Focus on functional groups instead of populations of species thus appreciating species redundancy in the delivery of the relevant ecosystem services for agricultural production.

**Indirect effects for NTAs.** Manage the complexity for indirect effects for NTAs and soil organisms since indirect effects are inevitable for all tools and practices in agriculture. Therefore, indirect effects of PPPs could be assumed as acceptable if the direct effects are considered acceptable and align with the efficacy requirements of Regulation 1107/2009.

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FOR MORE INFORMATION

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